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Serum Apelin Level in Type 2 Diabetic Mellitus Patients and Its Association With Metabolic Syndrome Components

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Abstract

Background: Metabolic syndrome (MetS) is a multiple risk factor for metabolic diseases. Apelin plays a crucial role in controlling insulin sensitivity and secretion in animals. The study aimed to clarify the difference in serum apelin between Iranain subjects with MetS and type 2 diabetes mellitus (T2DM), and subjects without MetS and its association with MetS components.

Methods: The study was conducted on 196 individuals, including 98 Iranian subjects with MetS and T2DM, and 98 age- and sex-matched individuals without MetS. MetS was defined using Adult Treatment Panel III (ATP-III) guidelines.

Results: Serum apelin level was significantly lower in subjects with MetS than those without MetS. There was a negative correlation between apelin and fasting blood glucose (FBG) in subjects with MetS and in both sexes ($P < 0.05$).

Conclusions: The apelin level in Iranian T2DM subjects with MetS is related to FBG. Apelin is thought to affect glucose metabolism and insulin resistance. Apelin may be an essential indicator in Iranian T2DM people and may play an important role in preventing diabetes complications in T2DM patients.

Keywords: Apelin; Metabolic syndrome components; Type 2 diabetic patients

Introduction

Metabolic syndrome (MetS) is a combination of clinical conditions including central/abdominal obesity, systemic hypertension, insulin resistance (IR) or type 2 diabetes mellitus (T2DM), and atherogenic dyslipidemia [1]. MetS is a multiplex risk factor for atherosclerotic cardiovascular disease (ASCVD) and T2DM. It doubles the risk for ASCVD and, in patients without diabetes, it increases the risk for T2DM five-fold [2]. MetS occurs commonly all over the world, ranging in prevalence from 30% to 40% [3]. MetS indicates a different prevalence in some other populations. Many studies have shown that MetS changes in different ethnic groups and gender [4-6]. It is reported that the MetS prevalence varies from 8% to 24% and from 7% to 46.5% among the males and females world population, respectively [7-9]. In European Americans and in the European population, the MetS prevalence is different from 20% to 30% in men and women [10-12]. It has shown that the prevalence of MetS is growing in Asian countries [13].

Apelin is made of a peptide of a 12-amino acid that is encoded by the APLN gene and expressed in human adipocytes [14]. Adipose tissue synthesizes and secretes bioactive hormones and mediators (adipokines) regulating metabolic activity. Apelin is one of the recently recognized adipokines in human adipocytes involved in many manifestations of MetS components related to obesity [15]. Apelin controls insulin sensitivity and secretion in animals [16]. Several studies, but not all, have reported that the elevation in apelin levels in humans and animals induces various metabolic diseases. Recently, apelin has been a prospective therapeutic target for various metabolic disorders such as diabetes mellitus, hyperinsulinemia and IR [17, 18]. Apelin has been characterized as a new adipokine in obese and hyperinsulinemic humans and mice. Apelin may prevent insulin secretion in mice. It seems that apelin plays an important role in regulation of glucose homeostasis [19]. Some studies on humans showed that injection of high doses of apelin causes elevation of insulin sensitivity and the apelin pathway in T2DM patients. It may be thought over as a new therapeutic target for various metabolic diseases [20]. It seems to be a helpful adipokine with anti-obesity and anti-diabetic characteristics [21]. Most of the studies reveal the controversial discussion around the levels of apelin and its associations with metabolic disorders. However, the level of apelin in diabetic patients is not exactly clear, because there are controversial findings among the various studies. Some studies reported that the level of serum apelin in subjects with MetS is higher than in healthy controls [21-25], while some other findings

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showed contrary results that serum apelin in T2DM and hypertension subjects was lower than in healthy controls [26-30]. According to controversial findings, this study aimed to determine the apelin levels in Iranian subjects with T2DM and MetS and compare them with those without MetS and to find out the associations between apelin levels and MetS components.

Materials and Methods

The present study was conducted at the Metabolic Disorder Research Center of Gorgan, Golestan province (Southeast of Caspian Sea), Iran between April and September in 2022. The Ethical Committee of Golestan University for Medical Sciences approved our study (IR.GOUMS.REC.1401.221). The study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. Oral consent was obtained from participants after an explanation of the purpose and procedures of the study. The study was conducted in 98 T2DM Iranian subjects with MetS and 98 age- and sex-matched subjects without MetS. The MetS subjects included 27 males and 71 females aged 26 - 77 years, ranging age 50 years. The group without MetS consisted of 31 males and 67 females aged 20 - 77 years, ranging age 47 years. The exclusion criterion was that T2DM subjects had no diabetic ketosis according to medical history and current treatment with an oral agent, no diabetic nephropathy or retinopathy complications and no administration of insulin. A blood sample was provided by all participants. The 5-mL blood samples were provided for all subjects after 12 h overnight fast. After the serum separation, it was used to determine biochemical parameters. Fasting blood glucose (FBG), triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) were measured by commercial kits using an automated method (Mindray BS-380/China) in a non-governmental laboratory. The remaining serum was kept at -20 °C for apelin activity test by a commercial kit (Bioassay Technology Laboratory, China) and enzyme-linked immunosorbent assay (ELISA) technique. Weight was measured by digital weight balance, all heavy clothing has been lifted, and light clothing has been restricted, with a loss of about 0.5 kg. Waist circumference (WC) was assessed midway between the iliac crest and the lower rib and measured by flexible measuring tape in centimeters. Body mass index (BMI) was calculated by dividing the weight (kg) by square body height (m^2). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) (mm Hg) were measured while taking into consideration resting approximately 5 min before measurement.

All subjects were taken into account to have MetS if they had three or more of the following criteria, according to the NCEP/Adult Treatment Panel III (ATP III) [31]: 1) Abdominal obesity: WC > 102 cm in males and > 88 cm in females; 2) Hypertriglyceridemia: serum TG level ≥ 150 mg/dL; 3) Low HDL-cholesterol: < 40 mg/dL in males and < 50 mg/dL in females; 4) High blood pressure: SBP ≥ 130 mm Hg and/or DBP ≥ 85 mm Hg or on treatment for hypertension; and 5) High FBG: serum glucose level ≥ 110 mg/dL or on treatment for diabetes.

Statistical analysis

The results were statistically presented and analyzed using SPSS software, version 17. The analysis was calculated as mean ± standard deviation (SD). The Shapiro-Wilk test was used to determine the normal distribution of data, and the Chi-squared test, analysis of variance (ANOVA), Spearman's rho, and Pearson's correlation coefficient were utilized as statistical tests to determine the relationship among parameters of the study. To assess correlations between serum apelin levels and the sum of metabolic parameters, a general correlation analysis (Mann-Whitney U/Spearman's rho) was carried out.

Results

Table 1 shows the distribution of frequency and percentage of MetS and its components in all study subjects. The percentages of subjects with one, two, three, four and five components of MetS were 14.28%, 30.1%, 17.34%, 27.04% and 5.61%, respectively. Of the subjects, 5.61% had no high or low (abnormal according to ATP-III criteria) components. The highest percentage was that of subjects with two components of MetS (30.1%). The subjects were more common associations in high WC, hypertension and hyperglycemia.

Table 2 shows the demographic and biochemical characteristics of the study population. The mean WC, SBP and DBP, TG and FBG levels were significantly higher in subjects with MetS than those with MetS, while the mean HDL-cholesterol and apelin levels were low ($P < 0.001$).

Tables 3 and 4 show the demographic and biochemical characteristics of the male and female subjects. In comparison between male subjects into two groups, FBG and TG in the subjects with MetS were significantly higher than in the subjects without MetS ($P < 0.05$), except HDL-C and apelin, while in female subjects WC, SBP, DBP, FBG and TG were significantly higher than in the subjects without MetS (except HDL-C and apelin) ($P < 0.05$).

Table 5 shows the correlations of apelin with MetS components in the subjects with MetS. Regarding correlation, apelin correlated significantly negatively with FBG ($P < 0.05$) of the subjects with MetS.

Table 6 shows the correlations of apelin with MetS components in the subjects with MetS according to sex. For male and female subjects with MetS, apelin correlated significantly negatively with FBG ($P < 0.01$).

Discussion

The study evaluated serum apelin levels in Iranian T2DM subjects with MetS compared to those without MetS. MetS may increase the risk of some diseases such as cardiovascular diseases, which may cause mortality. Although the pathogenesis of MetS is still not exactly known, apelin has been shown to have different effects on many organs and tissues, such as the brain, heart, gut, and kidney [32]. Apelin has been found in adipocytes, and this may clarify an endocrine role for apelin as an adipokine [33,

Table 1. Distribution of Frequency and Percentage of Metabolic Syndrome Components in Study Subjects

Metabolic syndrome components	Total subjects (n = 196)
No abnormal components, n (%)	11 (5.61)
One component (%)	28 (14.28)
High waist circumference	11 (5.61)
Hyperglycemia	5 (2.55)
Hypertriglyceridemia	6 (3.06)
Low HDL-C	6 (3.06)
Two components, n (%)	59 (30.1)
High waist circumference + hyperglycemia	14 (7.14)
High waist circumference + hypertension	2 (1.02)
High waist circumference + hypertriglyceridemia	14 (7.14)
High waist circumference + low HDL-C	16 (8.16)
Hyperglycemia + hypertension	3 (1.53)
Hyperglycemia + hypertriglyceridemia	2 (1.02)
Hyperglycemia + low HDL-C	1 (0.51)
Hypertriglyceridemia + low HDL-C	7 (3.57)
Three components, n (%)	34 (17.34)
High waist circumference + hypertension + hyperglycemia	6 (3.06)
High waist circumference + hyperglycemia + hypertriglyceridemia	5 (2.55)
High waist circumference + hyperglycemia + low HDL-C	5 (2.55)
Hypertension + hyperglycemia + hypertriglyceridemia	6 (3.06)
Hypertension + hyperglycemia + low HDL-C	4 (2.04)
Hyperglycemia + hypertriglyceridemia + low HDL-C	8 (4.08)
Four components, n (%)	53 (27.04)
High waist circumference + hypertension + hyperglycemia + hypertriglyceridemia	8 (4.08)
High waist circumference + hypertension + hyperglycemia + low HDL-C	5 (2.55)
High waist circumference + hyperglycemia + hypertriglyceridemia + low HDL-C	36 (18.36)
Hypertension + hyperglycemia + hypertriglyceridemia + low HDL-C	4 (2.04)
Five components, n (%)	11 (5.61)
High waist circumference + hypertension + hyperglycemia + hypertriglyceridemia + low HDL-C	11 (5.61)

HDL-C: high-density lipoprotein cholesterol.

Table 2. Demographic and Biochemical Characteristics of the Study Population

Parameters	With MetS (n = 98)	Without MetS (n = 98)	P-value
Age (years)	47.24 ± 10.70	46.75 ± 14.80	0.234
BMI (kg/m^2)	26.68 ± 5.30	26.5 ± 5.10	0.762
WC (cm)	105.10 ± 10.40	97.68 ± 13.60	< 0.001*
SBP (mm Hg)	126.0 ± 20.10	118.05 ± 15.18	0.002*
DBP (mm Hg)	81.90 ± 10.62	6.44 ± 6.94	< 0.001*
FBG (mg/dL)	173.80 ± 61.51	118.87 ± 65.20	< 0.001*
TG (mg/dL)	197.17 ± 88.10	128.84 ± 55.20	< 0.001*
HDL-C (mg/dL)	42.41 ± 9.29	46.7 ± 9.70	< 0.001*
Apelin (ng/mL)	229.18 ± 151. 24	429.90 ± 167.06	< 0.001*

Data are presented as mean ± standard deviation. Mann-Whitney tests were applied. *P-value < 0.01 is highly significant. BMI: body mass index; DBP: diastolic blood pressure; FBG: fasting blood glucose; HDL-C: high-density lipoprotein cholesterol; MetS: metabolic syndrome; SBP: systolic blood pressure; TG: triglyceride; WC: waist circumference.

Table 3. Demographic and Biochemical Characteristics of Male Subjects

Parameters	With MetS (n = 27)	Without MetS (n = 31)	P-value
Age (years)	47.8 ± 11.6	44.03 ± 4.59	0.307
BMI (kg/m^2)	28.77 ± 5.98	26.33 ± 4.65	0.058
WC (cm)	104.63 ± 9.17	99.58 ± 12.14	0.144
SBP (mm Hg)	124.26 ± 18.23	119.35 ± 15.3	0.097
DBP (mm Hg)	80.41 ± 9.93	75.9 ± 6.89	0.055
FBG (mg/dL)	171.5 ± 58.5	126.6 ± 79.5	< 0.001*
TG (mg/dL)	214.4 ± 108.68	151.68 ± 61.5	0.008*
HDL-C (mg/dL)	37.93 ± 6.0	41.58 ± 6.49	0.046**
Apelin (ng/mL)	203.66 ± 130.82	433.82 ± 209.32	< 0.001*

Data are presented as mean ± standard deviation. Mann-Whitney tests were applied. *P-value < 0.01 is highly significant. **P-value < 0.05 is significant. BMI: body mass index; DBP: diastolic blood pressure; FBG: fasting blood glucose; HDL-C: high-density lipoprotein cholesterol; MetS: metabolic syndrome; SBP: systolic blood pressure; TG: triglyceride; WC: waist circumference.

Table 4. Demographic and Biochemical Characteristics of Female Subjects

Parameters	With MetS (n = 71)	Without MetS (n = 67)	P-value
Age (years)	49.62 ± 10.23	47.90 ± 14.96	0.114
BMI (kg/m^2)	27.16 ± 5.12	26.60 ± 5.34	0.241
WC (cm)	105.30 ± 10.97	96.80 ± 14.53	< 0.001*
SBP (mm Hg)	126.6 ± 20.96	117.40 ± 15.18	0.003*
DBP (mm Hg)	82.50 ± 10.98	76.60 ± 7.0	0.002*
FBG (mg/dL)	174.60 ± 63	115.20 ± 57.85	< 0.001*
TG (mg/dL)	190.50 ± 78.8	118.20 ± 49.0	< 0.001*
HDL-C (mg/dL)	47.30 ± 26.7	50.20 ± 13.59	0.002*
Apelin (ng/mL)	238.90 ± 158.8	428.20 ± 145.2	< 0.001*

Data are presented as mean ± standard deviation. Mann-Whitney tests were applied. *P-value < 0.01 is highly significant. BMI: body mass index; DBP: diastolic blood pressure; FBG: fasting blood glucose; HDL-C: high-density lipoprotein cholesterol; MetS: metabolic syndrome; SBP: systolic blood pressure; TG: triglyceride; WC: waist circumference.

Table 5. Correlations of Apelin With Study Parameters in Subjects With and Without MetS

Parameters	With MetS (n = 98)		Without MetS (n = 98)	
	r	P-value	r	P-value
Age (years)	0.276	0.345	-0.357	0.245
BMI (kg/m^2)	0.030	0.767	0.130	0.201
WC (cm)	0.290	0.778	-0.021	0.838
SBP (mm Hg)	-0.003	0.975	-0.126	0.214
DBP (mm Hg)	0.079	0.443	0.113	0.270
FBG (mg/dL)	-0.294	0.003*	-0.166	0.129
TG (mg/dL)	-0.005	0.957	0.384	0.364
HDL-C (mg/dL)	0.199	0.086	-0.045	0.661

Correlation-Spearman tests were applied. *P-value < 0.01 is highly significant. BMI: body mass index; DBP: diastolic blood pressure; FBG: fasting blood glucose; HDL-C: high-density lipoprotein cholesterol; MetS: metabolic syndrome; SBP: systolic blood pressure; TG: triglyceride; WC: waist circumference.

Table 6. Correlation of Apelin With Study Parameters According to Sex With MetS

Parameters	Male		Female	
	r	P-value	r	P-value
Age (years)	-0.235	0.076	-0.111	0.197
BMI (kg/m^2)	0.009	0.949	-0.135	0.114
WC (cm)	-0.067	0.618	-0.201	0.180
SBP (mm Hg)	-0.138	0.301	-0.269	0.128
DBP (mm Hg)	-0.143	0.285	-0.089	0.300
FBG (mg/dL)	-0 .473	< 0.001*	-0.311	< 0.001*
TG (mg/dL)	-0.222	0.094	-0.124	0.148
HDL-C (mg/dL)	0.313	0.067	0.105	0.219

Correlation-Spearman tests were applied. *P-value < 0.01 is highly significant. BMI: body mass index; DBP: diastolic blood pressure; FBG: fasting blood glucose; HDL-C: high-density lipoprotein cholesterol; MetS: metabolic syndrome; SBP: systolic blood pressure; TG: triglyceride; WC: waist circumference.

34]. Several studies, though not all, have claimed that increased apelin levels in humans and animals cause various metabolic disorders. Apelin has come to light as a helpful adipokine with anti-obesity and anti-diabetic effects, making it a potentially effective therapeutic target for various metabolic complications [21]. In some studies, plasma apelin levels have been indicated to be increased in insulin-resistant subjects and in morbidly obese persons with T2DM when compared with normal controls [26, 35, 36]. Some studies have revealed that plasma apelin levels are decreased in newly diagnosed patients with T2DM [27, 28]. Some other findings revealed that T2DM was associated with increased serum apelin levels [37], while other studies indicated that apelin levels were significantly higher in T2DM patients than in control subjects in the general population [38]. It has been shown that increased levels of apelin are associated with reduced risk of T2DM progression [39]. A study on undiagnosed diabetic patients in Iran indicated that FBG and apelin were a subset of important characteristics that may have caused to understand the differences between diabetics versus non-diabetic obese women [40]. Apelin may be taken into account as one of the important prediction biomarkers for metabolic diseases. There are higher serum apelin levels in the group with MetS compared to those without MetS [22, 23]. It is worth mentioning that all subjects in these studies were without T2DM. At the same time, the participants in our study had T2DM before enrollment. In another study between children and adolescents, the level of apelin in obese children with and without MetS was found to be higher than in healthy children and adolescents. Knowing that this study was conducted for children and adolescents without diabetes [41], while our study was conducted on participants with T2DM and MetS aged between 20 and 77 years. Our study is also inconsistent with other findings [25]. They reported that serum apelin levels in T2DM with MetS subjects were higher than the control group. It should be mentioned that their T2DM issues were under therapeutic control, just like our patients' group. A study has revealed that the serum apelin level in T2DM patients who were morbidly obese was significantly higher than in healthy controls [26]. Therefore, the discrepancy in the results of these studies with our results may be attributed to the difference in participant numbers. Various studies are consistent with our findings. They concluded that the serum apelin level in subjects with T2DM was lower than healthy subjects. Some studies reported lower serum apelin levels in T2DM subjects compared to the control group [27, 28]. Onalan et al [29] also found that the level of apelin in the T2DM and MetS groups was lower than in control groups. Another study showed that serum apelin of T2DM with hypertension is more melancholy than healthy controls [30]. Some other studies were conducted on the newly diagnosed and untreated T2DM population. They reported that serum apelin levels at the baseline were higher in subjects with T2DM compared to the controls [41]. At the same time, the apelin levels at the end of the prescribed treatment period with the hypoglycemic agent for 6 months dropped and became lower than the level at the baseline. In contrast to our results, they revealed that newly diagnosed and uncontrolled diabetes patients with MetS have higher apelin levels. On the other hand, the apelin level significantly dropped after treatment, which was consistent with our results. The findings of some studies were consistent with our results [27, 28]. A study by Fan et al [42] on newly diagnosed T2DM revealed a contrary finding to other studies [41] when serum apelin levels in T2DM subjects were higher at baseline than in the control group. After treatment with hypoglycemic agents, the apelin level increases further. Some studies show that apelin is associated more with T2DM than with obesity [43]. Increased levels of apelin could be a compensatory mechanism to IR.

A study on a Chinese population revealed a gender-specific susceptibility of apelin to MetS prevalency and its components, which may be caused by change of apelin levels. Their study showed that apelin levels were significantly higher in MetS patients than controls in both sexes [44]. Studies by Angelova et al reported the same result for males [45]. Karbek et al also showed higher levels of apelin in MetS than age-matched controls. They indicated a positive relationship between apelin levels with IR [23]. The results of Yu et al showed significantly higher apelin levels in males with T2DM and MetS compared to the controls [41].

Our findings showed that apelin levels were lower in MetS patients than those without MetS in both sexes. Our results were not in agreement with their findings [41]. These findings may suggest that apelin can have important clinical implications for MetS. A study has shown that the apelin level was negatively correlated with FBG, and positively correlated with insulin sensitivity [29]. Our findings revealed that there was a negative correlation between apelin and FBG in subjects with MetS and also in both sexes. Some other studies have revealed that apelin levels were positively correlated with WC and BMI [17]. These findings were not in agreement with our results. Apelin has been demonstrated to be able to inhibit insulin secretion. This can cause insulin sensitivity and may suggest a role of apelin in insulin metabolism [46, 47]. The association between apelin with FBG in subjects with MetS at all may suggest that FBG might be taken into account as an important factor that may influence the serum apelin levels.

There were some limitations in the present study. Our data were enrolled in this area and this restricted our study results. There were also limited sample sizes for male subjects with and without MetS, because of causal sampling in our study.

Conclusions

The current study reported that T2DM with MetS in Iranian patients affected serum apelin levels, and apelin correlated with FBG. The regulation of glucose may influence apelin in T2DM. Correlation of apelin with some components of MetS can be a helpful marker in prevention of T2DM complications. Further studies may be necessary to evaluate serum apelin levels in subjects with and without MetS in relation to other diseases and may help us to assess a relationship between apelin in subjects with MetS and related diseases. Thus, the determination of serum apelin may contribute to the evaluation of the MetS occurrence in T2DM patients.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed consent was obtained from all individuals included in this study.

Author Contributions

AM conceived and designed the experiments. AM and HAHS analyzed and interpreted the data and wrote the article. MS and HAHS performed the experiments. AM, MT and NP contributed reagents, materials, and analysis data. All authors have accepted responsibility and approved its submission.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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